Ethical Issues in Human Subjects Research: Toxicogenomics and Molecular Epidemiology

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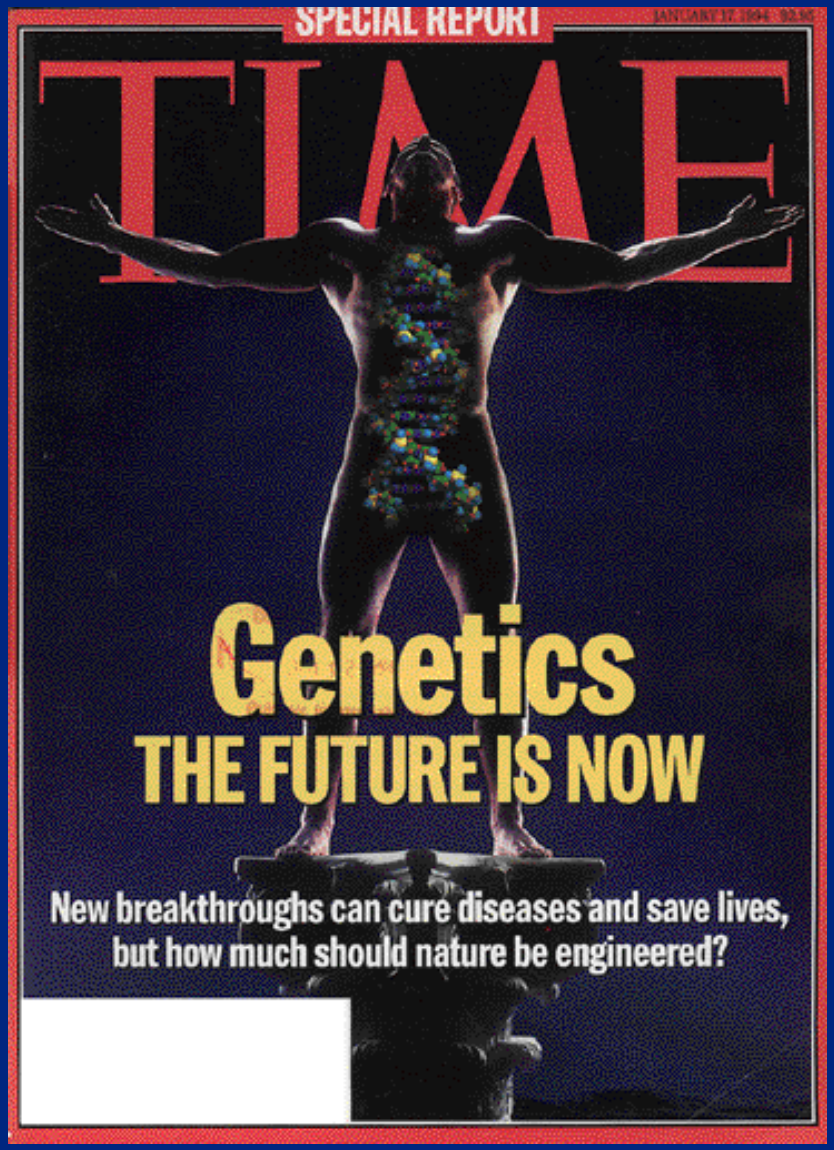
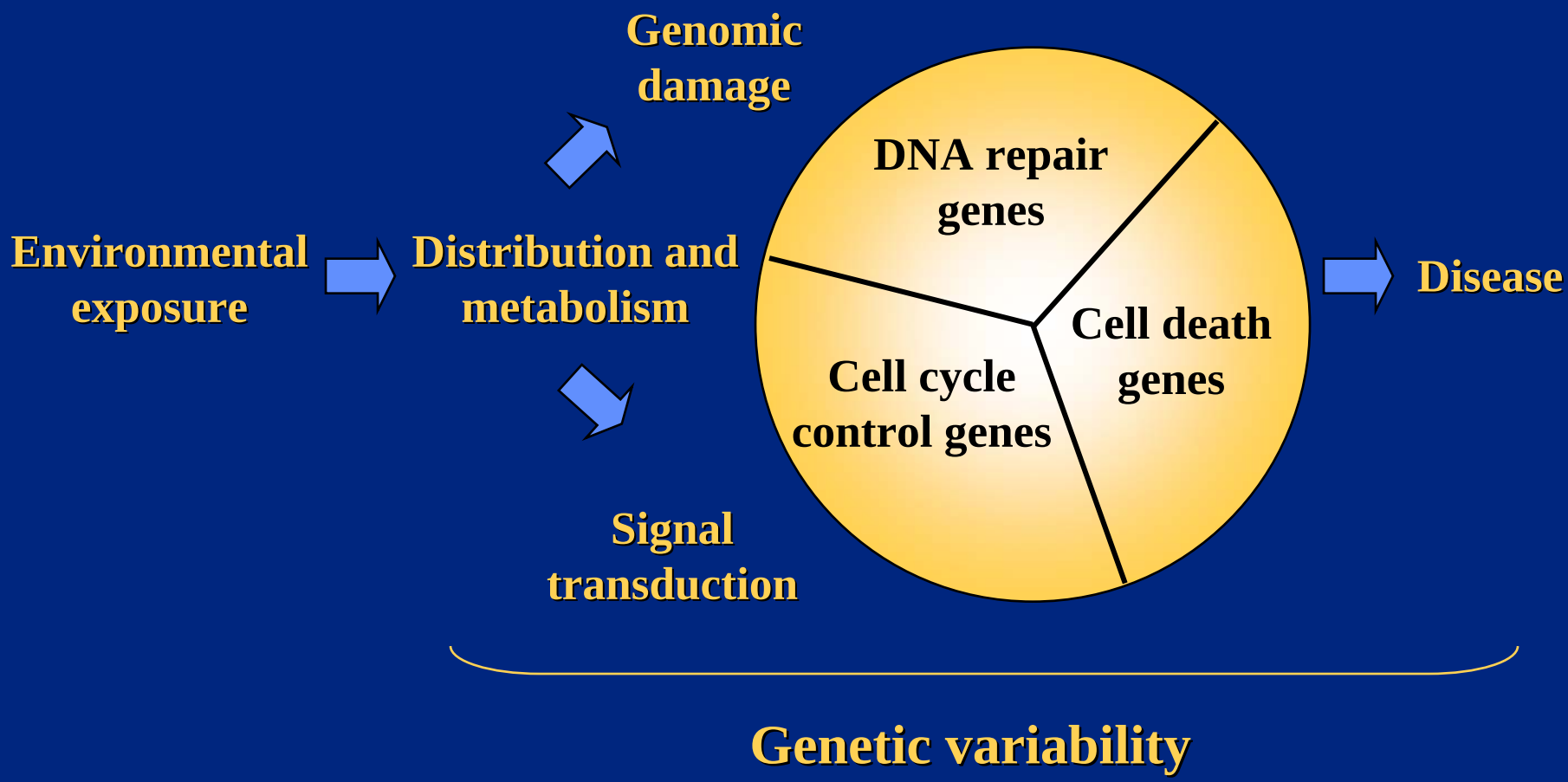
Overview

- Environmental health and genetics
  - Deciphering gene-environment interactions
  - Toxicogenomics defined
- Ethical issues in toxicogenomics and molecular epi
  - Questions about how researchers should present the promise and limitations of these new areas of research to the public
  - Potential misapplications of genomic information or technologies
  - The geneticization of environmental hazards and its implications for assignments of responsibility for poor health outcomes
  - Defining the scope of future research with biological materials


SPECIAL REPORT
TIME
Genetics
THE FUTURE IS NOW
New breakthroughs can cure diseases and save lives,
but how much should nature be engineered?

Changing Priorities in Genetic Research

Environmental Response Genes



“Environmental Response” Genes

Gene	Exposure	Disease
CYP2E1	benzene	leukemia
TGF-α	maternal smoking	facial clefts
NAT2	aromatic amines	bladder cancer

Applying Genetic Techniques in Toxicology: Toxicogenomics

Toxicogenomics can be defined as:

> "… the identification of potential human and environmental toxicants, and their putative mechanisms of action, through the use of genomic resources."

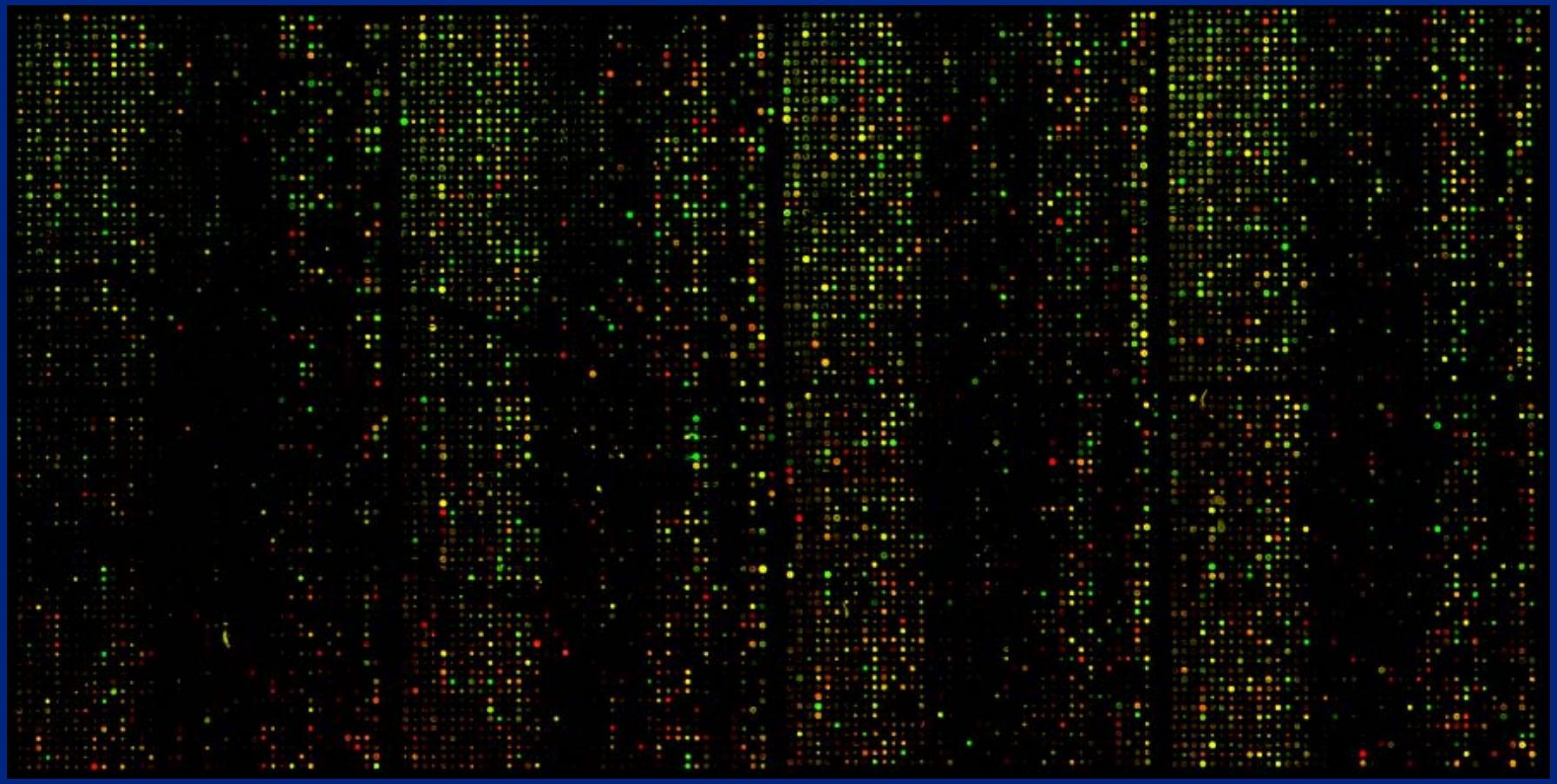
Nuwaysir EF, et al. Microarrays and Toxicology: The Advent of Toxicogenomics. Molecular Carcinogenesis 24: 153-159 (1999).

Applications of Toxicogenomic Technologies

Toxicogenomic tools could be applied in three areas relevant to the work done by the EPA:

- To identify individuals and subgroups at increased risk of disease (biomarkers of susceptibility)
- To identify persons exposed to an environmental hazard and/or assess the level of their exposure (biomarkers of exposure)
- To identify early disease processes before phenotypic changes are evident (biomarkers of early clinical effect)

cDNA Microarray Data



Source: Cindy Afshari, Ph.D.
National Center for Toxicogenomics

The Promise of Toxicogenomics

1. Cheaper way to assess the toxicity of chemicals, drugs, cosmetics, and environmental agents
2. Improve understanding of mechanisms of toxicity
3. Provide more precise estimates of exposure levels
4. Measure biological effects earlier, perhaps before evidence of toxicity
5. Identify unknown toxins (gene-expression and “toxic fingerprints”)
6. Identify individuals and subpopulations with increased sensitivity to chemicals, pharmaceuticals, cosmetics, etc.
7. Reduce number of animals used to evaluate chemical toxicity
8. Assist in setting regulatory standards

Ethical Issues in Toxicogenomics

1. How should scientists present the promise and limitations of emerging scientific technologies to the public?
2. How might toxicogenomic information (or technologies) be used in ways that are morally problematic?
3. How will knowledge of genetic sensitivities to environmental agents affect assignments of responsibility for poor health outcomes?
4. Defining the scope of future research with biological materials

Descriptions of Toxicogenomics

" … will likely contribute answers to some of toxicology's most fundamental questions."

"Toxicologists Brace for Genomics Revolution"

" … will have a dramatic impact on toxicology … "

" … promises new insights into mechanisms of drug action and toxicity."

" … a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process."

"Toxicogenomics is not a promise for the future, it is a tool that is available to us now …"

" … a tool of unprecedented power for use in toxicology … "

A Balanced Discussion?

- What are some of the limitations of toxicogenomic technologies?
- Why do the vast majority of media articles on toxicogenomics (and pharmacogenomics) fail to discuss these limitations?

Point 1: The growth of toxicogenomics provides an excellent opportunity to study the presentation of scientific findings to the public—and opportunities to improve the way science is presented.

  - Without a balanced discussion of these issues, it is likely that non-scientists will misinterpret the significance of toxicogenomic findings …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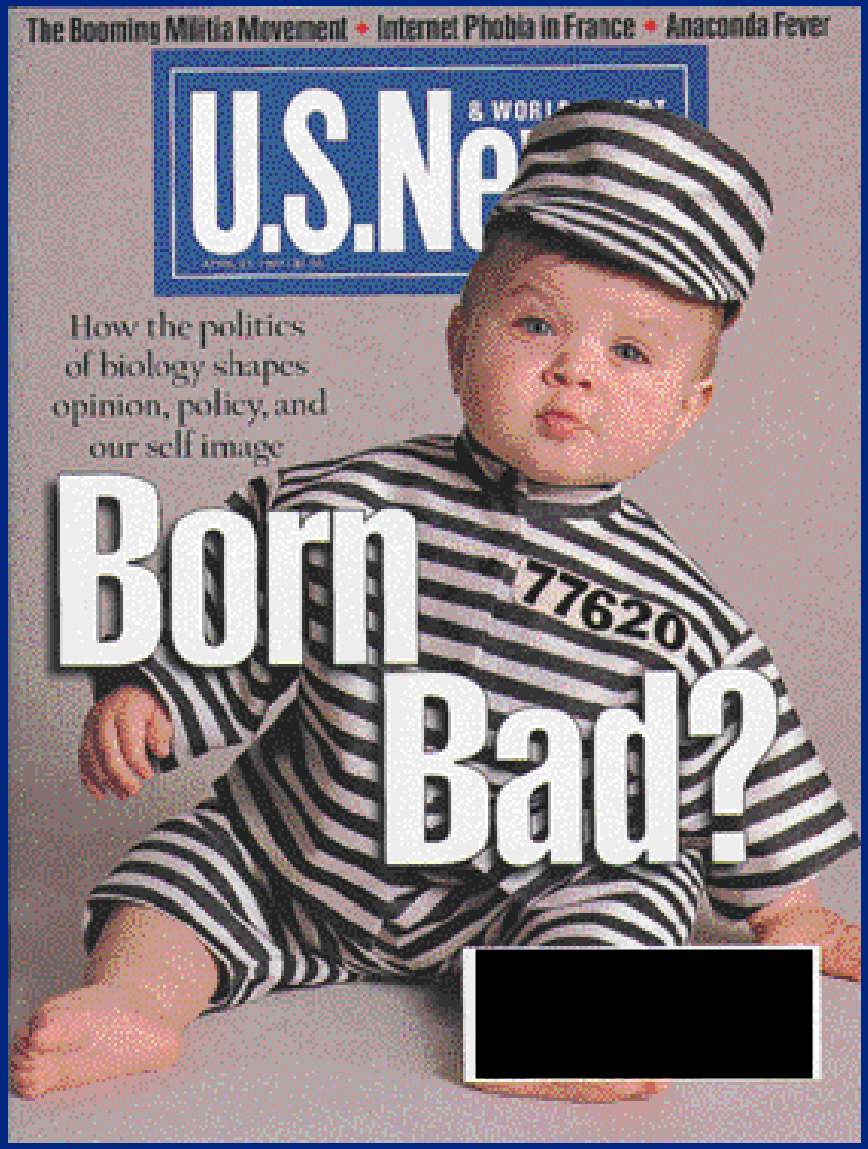
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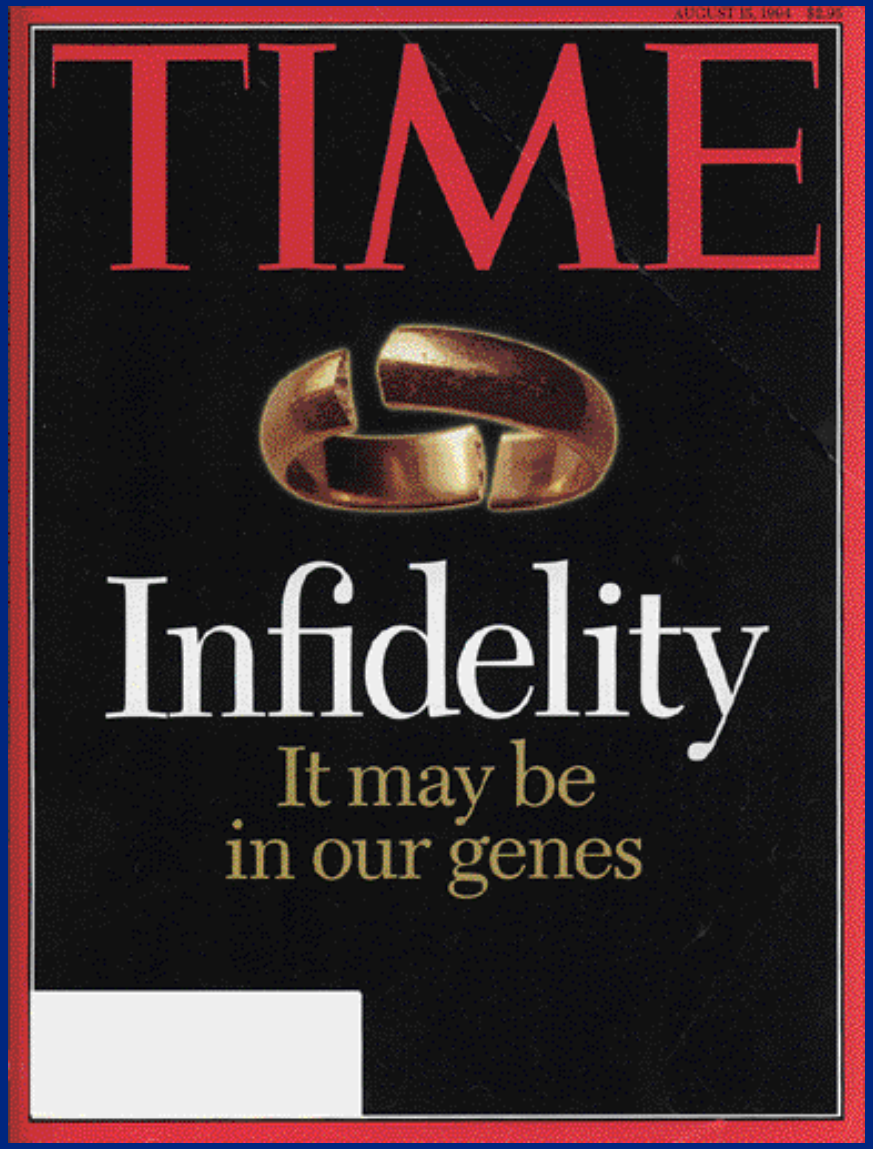
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It may be
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What's Different About "Environmental Response" Genes?

- The effects of environmental-response genes often depend upon the level of exposure, time of exposure, presence or absence or concurrent exposures, and variation in other sensitivity genes.
  - The biological implications of variation in these genes often is unclear (and far more complicated than familiar examples of genetic tests).
- The effects of environmental-response genes may be altered by changes in behavior or environmental conditions.
- Variation in environmental-response genes is much more common than the genetic variation associated with "disease genes".

New Discriminatory Challenges

Point 2: Since variability in sensitivity genes is common, but the biological implications of these genetic variants is often unclear, there is more opportunity for misuse of such genetic information (easy to find differences, difficult to interpret their meaning).

- Over time, will employers begin placing more emphasis on removing the “genetically vulnerable” worker instead of eliminating workplace hazards to which that worker may be sensitive?

The Burlington Northern Case

On February 12, 2001, following a suit brought under the ADA by the EEOC, Burlington Northern Santa Fe Railroad announced that it will no longer require employees who have submitted claims of work-related carpal tunnel syndrome to provide blood samples for genetic testing.

Employee Protections

- The testing was not intended to benefit the health or welfare of the employees tested.
- No informed consent was given for the genetic tests done by Burlington Northern.
- The tests themselves were scientifically questionable (associations not validated, predictive value unclear).
- It is not clear that Burlington Northern was doing anything illegal in conducting these tests.

Summary of Statutes Regarding Discrimination on the Basis of Genetic Information

Table 1. **Summary of Statutes Regarding Discrimination on the Basis of Genetic Information and the Privacy of Such Information.***

State or District	Health Insurance	Life Insurance	Employment	Confidentiality
Alabama	Yes, for cancer only†			
Alaska	Yes‡			
Arizona	Yes	Yes	Yes	Yes
Arkansas	Yes†‡		Yes	Yes
California	Yes§	Yes§	Yes	Yes
Colorado	Yes	Yes		Yes
Connecticut	Yes‡		Yes§	Yes
Delaware	Yes		Yes§	Yes
District of Columbia	Yes‡			
Florida	Yes‡			Yes
Georgia	Yes			Yes¶
Hawaii	Yes†‡§			
Idaho	Yes‡			
Illinois	Yes‡			Yes
Indiana	Yes†§			Yes
Iowa	Yes†‡		Yes†	
Kansas	Yes†§		Yes†	
Kentucky	Yes†‡			
Louisiana	Yes†		Yes	Yes
Maine	Yes‡	Yes	Yes†	
Maryland	Yes†	Yes	Yes†	
Massachusetts	Yes†	Yes	Yes	Yes
Michigan	Yes†		Yes†‖	
Minnesota	Yes†§		Yes†	
Mississippi				
Missouri	Yes†		Yes	Yes
Montana	Yes†‡¶	Yes		
Nebraska	Yes‡		Yes†‖	
Nevada	Yes†‡§		Yes†	Yes
New Hampshire	Yes†	Yes	Yes	Yes
New Jersey	Yes‡	Yes	Yes	Yes
New Mexico	Yes‡			Yes¶
New York	Yes		Yes	Yes
North Carolina	Yes		Yes	
North Dakota	Yes‡			Yes
Ohio	Yes†‡			
Oklahoma	Yes†‡		Yes†	Yes†
Oregon	Yes		Yes†	Yes
Pennsylvania				
Rhode Island	Yes		Yes	
South Carolina	Yes§			Yes
South Dakota	Yes†‡		Yes	Yes
Tennessee	Yes‡			
Texas	Yes**		Yes	Yes¶
Utah	Yes		Yes	Yes
Vermont	Yes†	Yes	Yes†	Yes
Virginia	Yes§		Yes	
Washington				
West Virginia	Yes‡			
Wisconsin	Yes†	Yes	Yes†‖	
Wyoming	Yes‡			

* Yes indicates that the state has enacted legislation concerning the use of genetic information in the indicated circumstance. This table was compiled in June 2003. Because these are areas of intense legislative activity, the laws change frequently. In addition, the laws vary far more widely from state to state than can be reflected in a table such as this. This table is not intended to be a legal opinion about the coverage of these laws. Readers are encouraged to consult the laws in their own states.
† Testing cannot be required.
‡ According to the statute, genetic information cannot be considered to indicate a preexisting condition in the absence of symptoms.
§ The statute specifically addresses illnesses in family members.
¶ The statute contains exemptions about the use of information for certain research and other purposes.
‖ Testing can be required for certain purposes, such as evaluating workers' compensation claims or surveillance.
** The statute permits testing to be required under certain circumstances.

Clayton, New Engl J Med 2003

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Example: Chronic Beryllium Disease

Randall White has been offered a job at a DOE weapons facility in New Mexico. Mr. White is excited about the new position, but after reading a local newspaper article on the harmful effects of beryllium, he's a little concerned about the new job, which will involve some beryllium processing. At a recent doctor's visit, Mr. White discusses these concerns with his physician, who suggests that he consider several genetic tests that could be done to help assess his likelihood of developing beryllium-associated disease.

After giving much thought to whether he should be tested, White decides to have the tests, which reveal that he is at increased risk of developing beryllium sensitization and chronic beryllium disease. Despite this knowledge, White decides to "let the chips fall where they may" and accepts the new position. He subsequently develops chronic beryllium disease within a year of assuming his new position.

Allegations that an Individual Has Made a Genetically Irresponsible Choice

1. Failing to act on information about one's genetic risks
   - Dismissing one's genetic risks as irrelevant or insubstantial
2. Failing to obtain information about one's genetic risks
   - Forgoing a genetic test that would shed light on an important aspect of one's actions
3. Failing to reveal one's genetic risks to others
   - Special variant of the above form of irresponsibility (e.g. failing to tell a spouse about a known genetic risk)

Problems in Assigning Responsibility for Poor Health

Excusing conditions:

- The choice may not have been fully voluntary (e.g. Mr. White's employment options may be severely limited).
- The choice may not have been fully informed (e.g. Mr. White may not understand the information provided by his physician).

Justifying conditions:

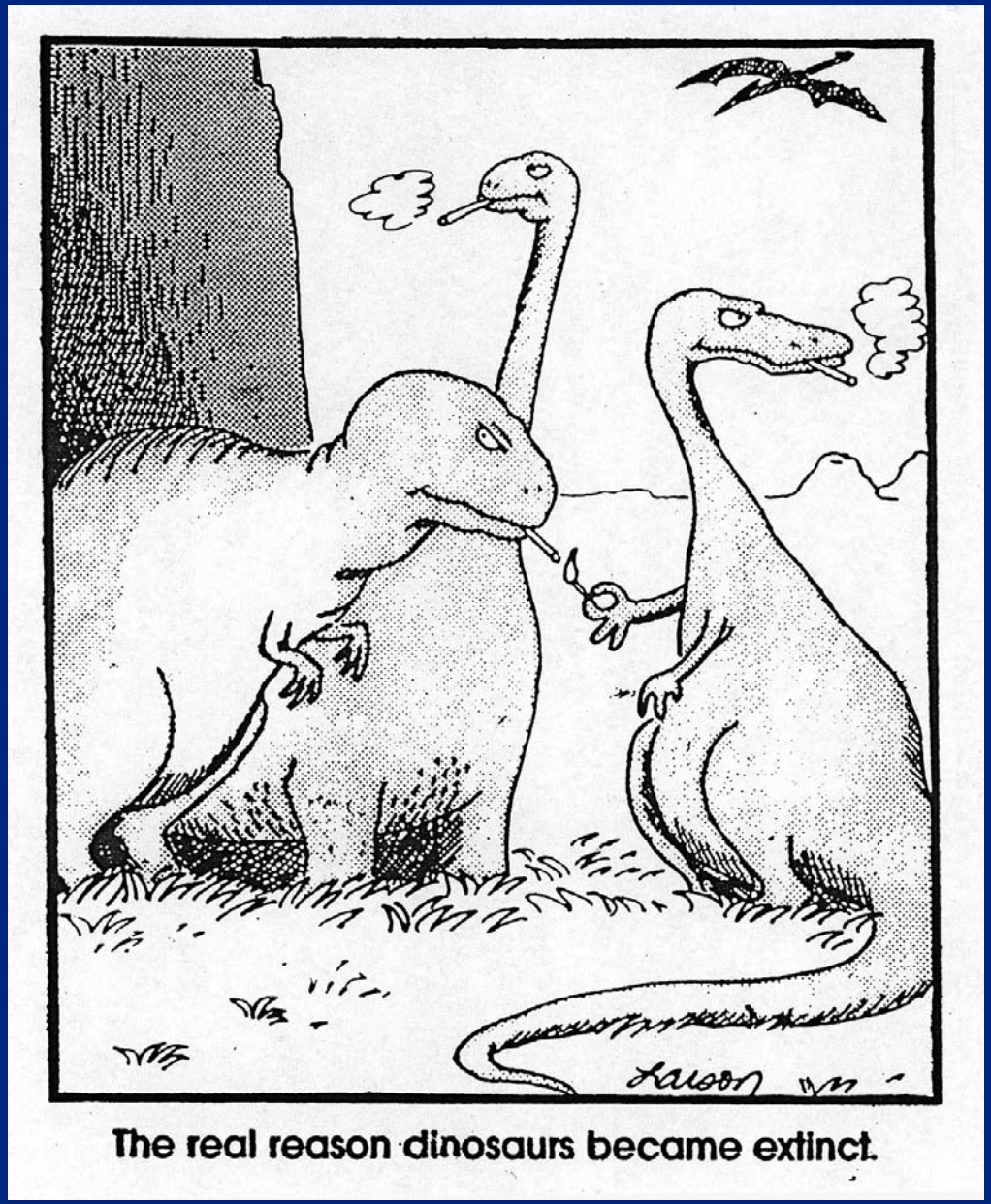
- The choice may be reasonable in light of the circumstances (e.g. Mr. White may believe personal or family interests justify the increased risk of poor health).

Defending an Allegation of Genetic Irresponsibility

Defending a judgment of genetic irresponsibility will require knowledge of many contextual features of the action, as well as some insight into how the actor weighed these consideration before choosing to act.

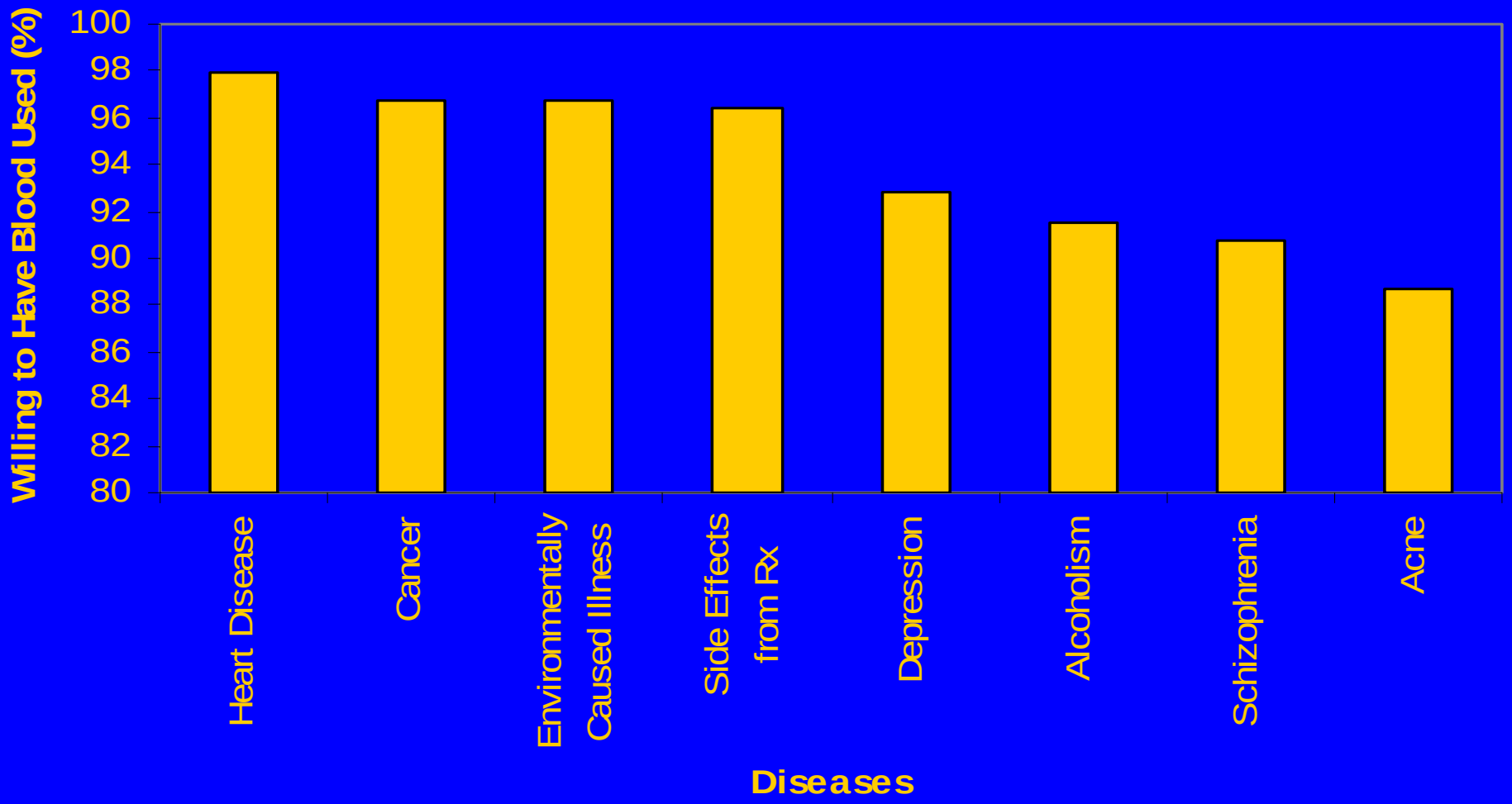
Point 3: Since we rarely have such detailed information, we should be cautious in making assertions of genetic irresponsibility, realizing that they often may be defeasible by various excusing conditions or act-justifying considerations.

… but, it's doubtful that we'll exercise such caution:



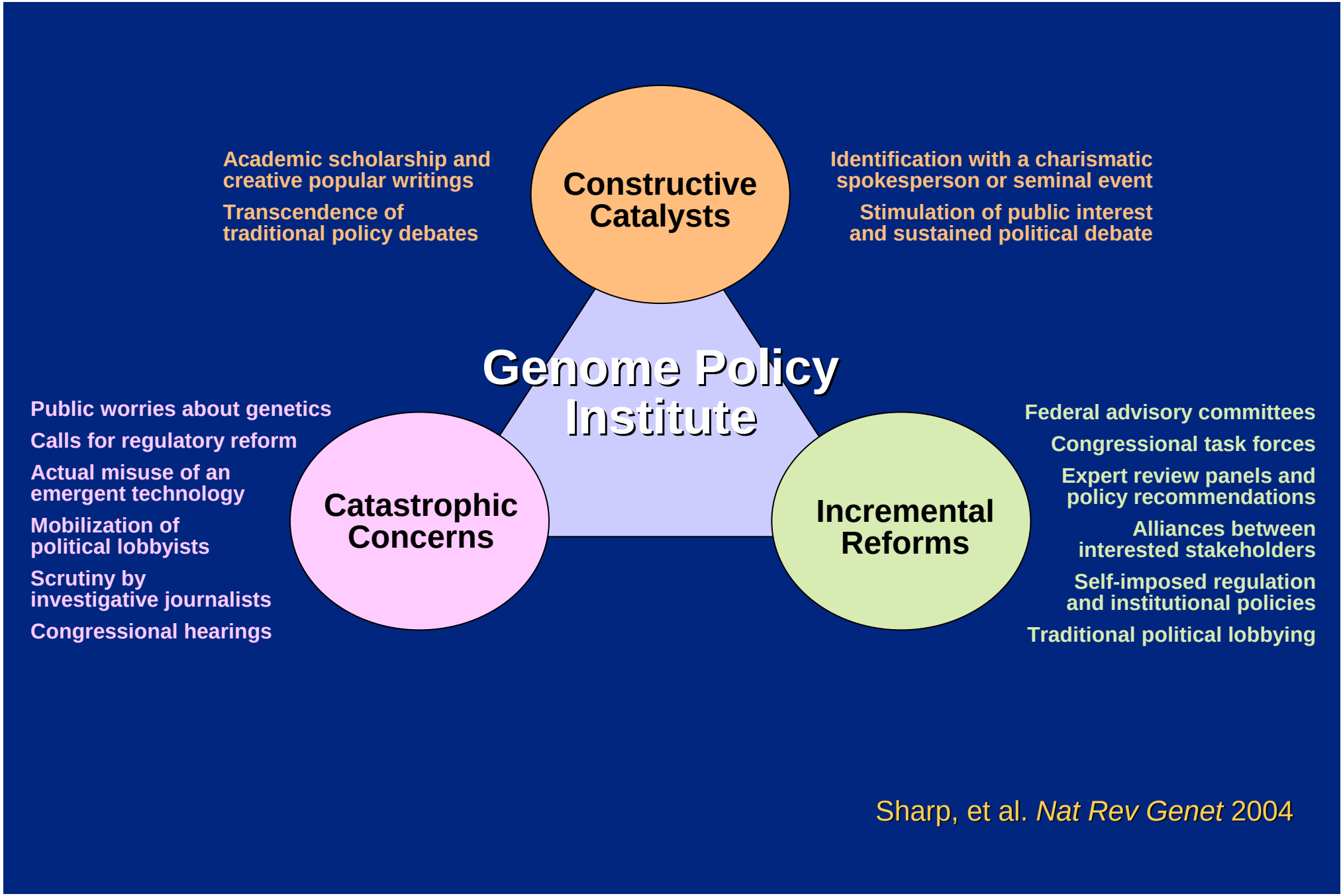
The real reason dinosaurs became extinct.

Donor Attitudes Regarding the use of Stored Biological Materials for Genetic Research on Specific Conditions

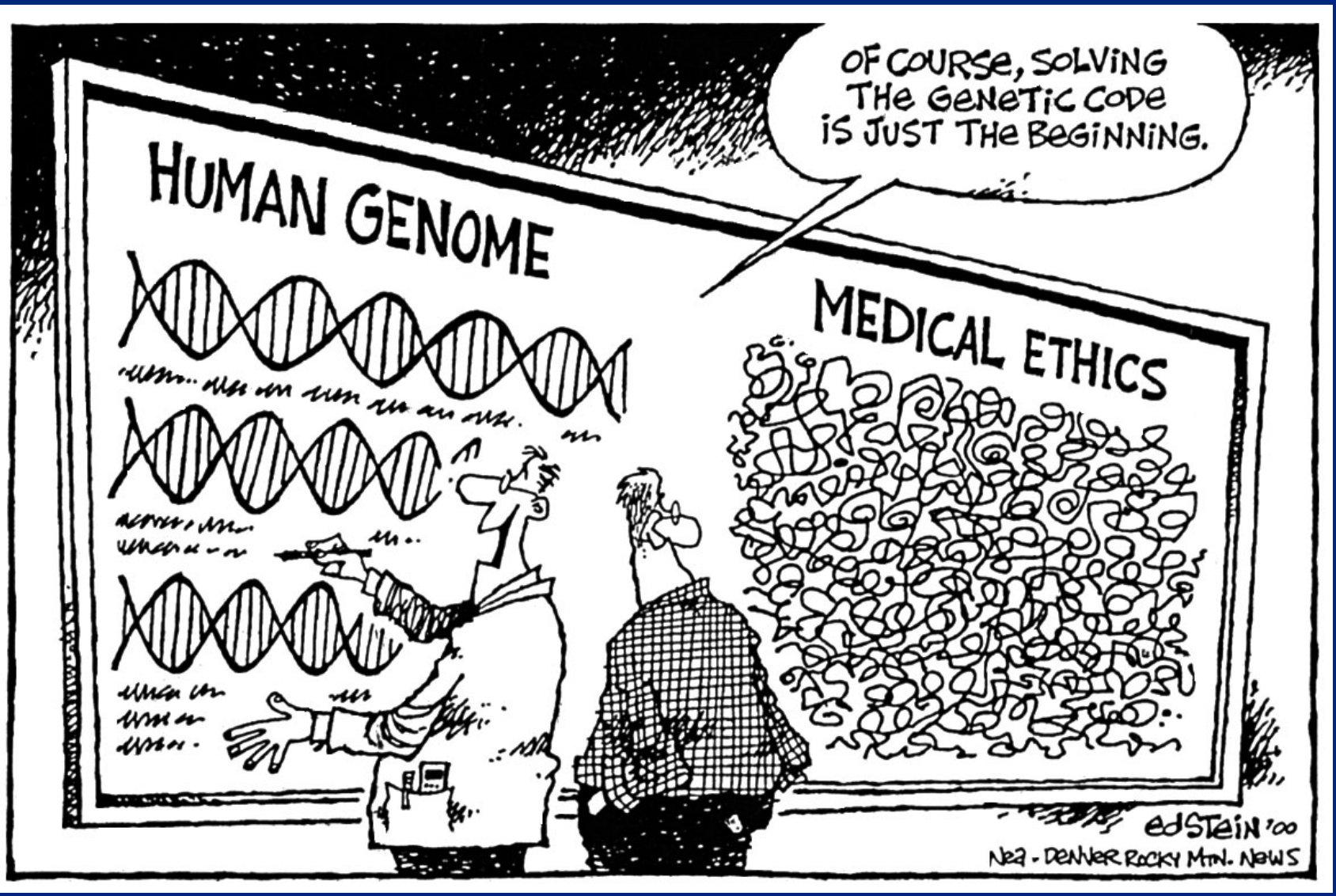


“Conclusions”

- The application of genetic technologies to environmental protection will introduce a number of ethical challenges for researchers and policy makers:
  - Presentation of scientific findings to the public,
  - Potential discriminatory threats,
  - How we think about assignments of responsibility for health outcomes, and
  - How we define the scope of future research with biological materials
- How best to develop appropriate policy responses to these ethical challenges remains unclear (ELSI-type program?)



Sharp, et al. *Nat Rev Genet* 2004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